Remarks

Applicants have cancelled the non-elected claims 15-16, 18-20, and 23-28, which were withdrawn as a consequence of election. Applicants reserve the right to pursue the subject matter of the cancelled claims in future applications.

Applicants have further cancelled claim 11.

Applicants have amended claims to recite to "mesechymal stem cells" instead of "MCSs" as suggested by the examiner. Support for the amendment is found at page 4, line 25, paragraph [0030]. Accordingly, no new matter has been added by this amendment and its entry is respectfully requested.

Applicants have further amended claim 1 to delete the term "top surface" and replaced it with the term "surface." Support for this amendment can be found throughout the specification, and particularly, for example, at page 18, lines 20-23, paragraph [0092]. Accordingly, no new matter has been added by this amendment and its entry is respectfully requested.

Applicants have amended claim 12 to recite to the second population of mesenchymal stem cells being loaded within "porous scaffold of said polymer" instead of reciting to "in the remaining volume of said matrix." The amendment is supported throughout the specification, and particularly, for example, at page 18, lines 20-23, paragraph [0092] and at page 21, lines 3-6, paragraph [0099]. Accordingly, no new matter has been added by this amendment and its entry is respectfully requested.

Applicants have amended claims 12 and 13 to recite to osteoinductive growth factor wherein the osteoinductive growth factor is BMP-2. This limitation was the

subject matter of the cancelled claim 11. Accordingly, no new matter has been added and the entry of the amendment is respectfully requested.

Applicants have further amended claim 13 to depend on claim 1 instead of claim 12. Support for this amendment can be found throughout the specification, and specifically, for example, at page 9, lines 23-27. Accordingly, no new matter has been added and the entry of the amendment is respectfully requested.

Applicants have amended the specification by a substitute paragraph [0046]. The text referring to Figures 4K and 4L has been deleted as no such figures were submitted with the original filing. The undersigned states that the amendment does not introduce new matter. Accordingly, the entry of the amended paragraph [0046] is respectfully requested.

Applicants submit a substitute paper copy of the Sequence Listing, a computer disk and a Statement stating that the paper copy and the disk are the same. No new matter has been added by the virtue of the substitute paper copy of the Sequence Listing and its entry is respectfully requested.

Applicants also submit a set of formal drawings wherein the defect in the Figure 3 has been corrected. The undersigned states that no new matter has been added by the substitute formal drawings and their entry is respectfully requested.

Turning now to the specific rejections.

Claims 1-14, 17, and 21-22 were rejected under 35 USC § 112, second paragraph. The examiner contends that certain terms or phrases used in the claims were vague. Such

terms and phrases included "top surface", "to elicit osseointegration", "cell-matrix structure", and "high-density cell pellet."

Claims 1, and 2-14 were rejected under 35 USC § 112, second paragraph, because of the term "top surface." Applicants respectfully submit that a skilled artisan would know what the "top surface" in the claims refer to. The term "top surface" defines the outer surface of the polymeric matrix block that would form the articular cartilage replacing surface. The claims describe a method of "coating" the matrix block so that the cells can form the cartilage matrix on the surface of the cell-polymer block. However, to expedite prosecution, applicants have amended the claims to refer to "surface" only. Applicants respectfully submit that the term surface accurately and specifically defines the location of cells with respect to the matrix block, and that the rejection of claims 1, and 2-14 under 35 USC § 112, second paragraph, should therefore be withdrawn.

Claims 10, 11, 12, 13 and 14 were rejection under 35 USC § 112, second paragraph, because of use of the phrase "to elicit osseointegration." Applicants respectfully disagree. The term "osseointegration" is well known in the art of tissue implants (see, e.g., Exhibit A). Therefore, one skilled in the art even without having read the specification would know that to "elicit osseointegration" as used in claim 10 refers to the capacity of the cells that are inoculated inside the polymeric matrix, as opposed to the surface of the polymeric matrix, to secrete growth factors, for example, to enhance the integration of the polymer-cell implant into the craft site. Accordingly, applicants respectfully submit that the rejection of claims 10, 11, 12, 13 and 14 under 35 USC § 112, second paragraph, should be withdrawn.

Claim 12 was rejected because of the limitation "the remaining volume" had no antecedent basis. To expedite prosecution, applicants have amended the claim to recite to a second population of cells that are loaded within porous scaffold of said polymer block. Applicants submit that the amendment overcomes the lack of antecedent basis for the terms and that accordingly, the rejection of claim 12 under 35 USC § 112, second paragraph, should be withdrawn.

Claim 13 was also rejected as being vague. To expedite prosecution, applicants have amended claim 13 to depend on claim 1. Accordingly, claim 13 now recites the graft construct as comprising of polymer matrix, mesenchymal stem cells pressed on the surface of said polymer matrix, which construct further comprises an osteoinductive growth factor. Accordingly, applicants submit that the rejection of claim 13 under 35 USC § 112, second paragraph, should be withdrawn.

Claims 17 and 21-22 were rejected under 35 USC § 112, second paragraph, because of the use of the phrase "cell-matrix structure." Applicants have amended the claim to recite to "cell-polymer structure" which is used throughout the claims. Accordingly applicants submit that the rejection of claims 17 and 21-22 under 35 USC § 112, second paragraph, should be withdrawn.

Claim 17 was further rejected under 35 USC § 112, second paragraph, because the examiner contends that the phrase "high-density cell pellet" is vague. Applicant respectfully disagree. The term "high-density cell pellet" is widely used in the art and generally refers to cell density exceeding than 5 million cells per ml. Such designation is derived originally from studies using embryonic pre-cartilage progenitor cells. See, for example, San Antonio JD, Tuan RS. Chondrogenesis of limb bud mesenchyme in vitro:

stimulation by cations. Dev Biol. 1986 115:313-324; DeLise AM, Stringa E, Woodward WA, Mello MA, Tuan RS. Embryonic limb mesenchyme micromass culture as an in vitro model for Chondrogenesis and cartilage maturation. Methods Mol Biol. 2000;137:359-375; and Johnstone, B., Hering, T. M., Caplan, A. I., Goldberg, V. M., and Yoo, J.U. (1998) In vitro chondrogenesis of bone marrow-derived mesenchymal progenitor cells. Exp. Cell Res. 238, 265-272. Copies of the articles are attached herewith.).

Accordingly, applicants submit that a skilled artisan would know the amount of cells needed in the claimed constructs, and that the rejection under 35 USC § 112, second paragraph, should therefore be withdrawn.

Claim 17 was further rejected under 35 USC § 112, second paragraph, as vague because of the use of terms first and second period of time. Applicants respectfully disagree. Applicants submit that claim 17 clearly recited that the first period of time refers to a time period that is sufficient to allow attachment of the pressed cells to the polymer surface and the second period of time should be sufficient to allow formation of cartilage on top of the attached cells. Applicants submit that a skilled artisan making such grafts would know how to determine when the cells are attached on the surface and how to determine when cartilage layer has been formed. Applicants describe that after pressing and culturing the cells for a first time period, cells that are not attached are removed (see, e.g., page 12, lines 19-20). Applicants further teach that the constructs with the attached cells are consequently (second time period) cultured in a chondrogenic medium to allow formation of cartilage layer. Applicants submit that detecting whether a cartilage layer has been formed includes routine analysis of the graft including, for example, histochemical and immunohistochemical analysis and scanning electron

microscopic analysis exemplified in the specification (see, e.g., page 13-14, paragraph [0076], and p. 17, lines 1-16, paragraph [0085]). Applicants respectfully submit that without undue experimentation and relying the examples provided in the specification, a skilled artisan can readily determine and optimize such first and second time periods for the specific conditions used in preparing the grafts. Applicants respectfully submit that knowing the variables in the biological processes, it would be unequitable to limit the claims to any specific times used in the examples.

Claims 10, and 12-13 were rejected under 35 USC § 112, first paragraph. The examiner contends that the disclosure does not provide guidance as to other "osteoinductive growth factors" than BMP-2. Although the terminology and use of osteoinductive growth factors are widely used and known to one skilled in the art, to expedite prosecution, applicants have amended claim 10 to recite to osteoinductive growth factors, wherein said osteoinductive growth factor is BMP-2. Consequently claim 11 has been cancelled as redundant. Accordingly, applicants submit that the rejection under 35 USC § 112, first paragraph, be withdrawn.

Claims 1-4 and 7-14 were rejected under 35 USC § 102(b) as unpatentable over Valentini and Kim ("Valentini"). The examiner argues that Valentini describes all elements of this invention disclosing a porous biodegradable matrix and mesenchymal stem cells that can serve as a substrate to, for example, mesenchymal stem cells, wherein the "surface of the polymer is contacted with the cells." Examiner further contends that the specification does not define what press-coating is.

Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

The unique aspect of the present grafts and methods of making such grafts is that the cells are first pressed on the scaffold and then cultured before implantation to allow formation of **cartilage layer** on the polymer surface before its implantation. The specification particularly teaches that it is the object of the invention to provide an in vitro prepared graft containing a cartilage layer (page 3, lines 28-29). Further, applicants submit that the specification particularly teaches that the polymer blocks are "gently pressed onto... cell pellet" (page 12, lines 7-9), and again that the "polymer blocks... were placed onto the cell pellets" (page 16, lines 12-13). Such descriptions clearly teach that the polymer block is pressed on the cells *in vitro*.

Valentini does not teach an engineered graft wherein a polymer scaffold press-coated with cells and contains a **cartilage layer**. Valentini teaches that the "scaffolds may be coated with a variety of materials, including bioactive agents, and bioerodable agents" (col 6, lines 19-21). Nowhere in the specification does Valentini teach that the scaffolds be coated by pressing cells on the scaffolds not to mention description of forming a cartilage layer on top of the polymer scaffold in vitro before implantation. Therefore, applicants respectfully submit that Valentini does not anticipate claims 1-4 and 7-14 and that the rejection under 35 USC § 102(b) be withdrawn.

Claims 5 and 17 were rejected under 35 USC § 103(a) as unpatentable over Valentini in view of Brekke and Toth ("Brekke") and Hung and Lo ("Hung").

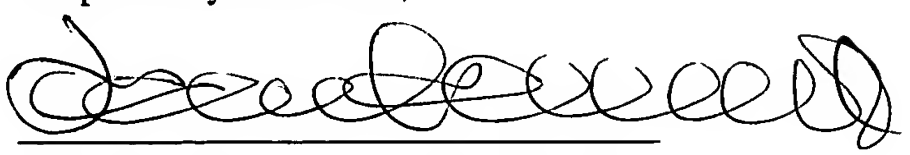
Applicants respectfully disagree and submit that the rejection be withdrawn for the following reasons.

To show *prima facie* case of obviousness the combination of references must teach all the elements of the claims (MPEP 2143). As discussed above, and incorporated herein by reference, Valentini does not teach an engineered graft press-coated with cells containing a cartilage layer. Neither Brekke nor Hung overcomes this deficiency. Brekke teaches a "composite device consisting of D,D,-L,L-polylactic acid macrostructure optimized to the architecture of cancellous bone, a microstructure composed of a filamentous velour of hyaluronan and a recombinant human bone morphogenetic protein 2..." (Abstact) Construct according to Brekke have a D,D,-L,L-polylactic acid macrostructure filled with hyaluronan and soaked with BMP2. Brakke does not disclose engineering a graft by pressing cells onto the polymer allowing growth of a cartilage layer on the graft before implanting. Hung teaches isolation of mesenchymal stem cells (MSCs) by seeding a porous culture plate with a mixture of cells comprising MSCs (see, e.g., paragraphs [0023] and [0025]). Nowhere does Hugh teach that isolated MSCs be pressed on polymer constructs to produce a graft with a cartilage layer.

Accordingly, the cited references do not even in combination teach all the elements of the claims and therefore, the rejection of claims 5 and 17 under 35 USC § 103(a) as unpatentable over Valentini in view of Brekke and Toth ("Brekke") and Hung and Lo ("Hung") should be withdrawn.

In view of the foregoing, applicants respectfully submit that all claims are now in condition for allowance. In the event of questions, the Examiner is kindly asked to contact the undersigned. Early and favorable action is earnestly solicited.

Respectfully submitted,



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